

as were the distribution of frequency with which individual muscles were injected, and the doses used in each.

SAFETY RESULTS

There were no deaths during this study. There were two subjects with serious adverse events. One female subject with a history of uterine bleeding had recurrence, and underwent elective hysterectomy. This subject withdrew from the study subsequent to the AE. One male subject had severe chest pain, was evaluated and hospitalized for this, and subsequently diagnosed as esophagitis.

Table 25: Adverse Event Incidence of at least 5% Rate - Study 004		
AE	% Within 6 wks	% Within 12 wks
Dysphagia	19	19
Neck Pain	9	10
Muscle Weakness	9	9
Headache	6	6
URI	6	10

All dysphagia events had onset within 6 weeks of treatment. Incidence rates by severity were 16% mild, 3% moderate. There were no severe dysphagia events reported.

Comment:

While the distribution of intensity does not raise especial new concerns, the absolute incidence of dysphagia is approximately twice that which was seen in Study 140, the only source of well conducted study data. This is entirely parallel to the [redacted] to [redacted] comparison that was performed for blepharospasm, at the time of initial distribution of [redacted]. In that comparison study the AE incidence for ptosis was increased with [redacted] toxin. Adding import to this comparison is that both of the primary concern AEs for these indications (dysphagia for cervical dystonia and ptosis for blepharospasm) are believed to be due to regional spread of toxin from the site of injection to adjacent muscles.

DISEASE ASSESSMENT STUDY OUTCOMES

The mean change in CDSS to week 6 was -5.2 points (median change -5). The mean change in Pain Frequency was -0.7 points, and mean change in Pain Intensity was -0.7 as well (median change was -0.5 for both).

Comment:

These open label response characteristics are similar to that seen in Study 140 for Period I, although not for Period II. This suggests that the efficacy response was not diminished with [redacted] toxin. However, there is no indication that it is increased either, as open label treatment responses of the same size were seen in Study 140.

STUDY 191622-014

OVERVIEW

This study was initiated after discussions between Allergan and CBER that ensued after Study 004 was completed and preliminary results examined. The dysphagia rate seen in Study 004 was higher than that seen in Study 147 with □---- derived Botox. This raised concern of an increased incidence of dysphagia with the new Botox. While the adverse events in-and-of themselves were neither highly frequent nor severe, in light of the modest degree of efficacy shown in Study 147 to be associated with Botox there was concern that the modest change in AE rates might change the risk-benefit comparison for □----- Botox from that of □---- Botox. Discussions between Allergan and CBER led to the design of Study 191622-014, hereafter called Study 014. This study was devised to provide indirect evidence that the patient's assessment of the risk-benefit comparison had not significantly altered. This would be achieved by comparison of the reported AE rates across 4 consecutive toxin treatment sessions, the first part being the subject's last 2 sessions in which they received □---- Botox, followed by subject's first two treatments with □----- Botox. Assessment of the dose of toxin received at the session following each of these key treatment sessions would provide confirmatory information regarding the acceptability of the response following the session. Allergan and CBER agreed that for this study, a retrospective review of charts kept for each physician's usual practice of clinical care would be a suitable basis for this study.

Comment:

CBER recognized that AE reporting would not be as rigorous in clinic medical records for treatment not within a study compared to AE reporting in a prospective study. However, it was not likely to be biased between the sessions, events of major clinical importance were likely to be noted in chart records, and thus the relative rates of AEs were likely to be reliable.

Title: A multicenter, retrospective study of the clinical experience of patients who had received new bulk toxin Botox and □---- Botox serially for the treatment of cervical dystonia based on a review of randomly selected charts.

CLINICAL STUDY DESIGN

Objective

The stated study objective was to evaluate the comparative safety of BCH2024 Botox and □---- Botox in clinical use in patients with CD.

General Design Structure

This study was a retrospective chart review of patients who had received treatment with the new commercial lots of Botox from bulk product lot □----- after receiving □---- Botox. The chart review focussed upon examining for explicit notations of adverse events, which would have been recorded according to each individual physicians' normal practice of clinical care. The study was also to examine for any significant changes in dosage associated with the change from □1 toxin to □----- toxin.

Each activated site was to provide to Allergan a list of all patients who received [redacted] Botox between January 1, 1998 and March 27, 1998 (at least 60 patients per site). Allergan randomized the patient list, and returned the random order list to the investigator. Investigators then performed chart reviews on the patients in the order of randomized list. Charts were first examined for eligibility. Eligible charts were then deemed to be enrolled into the study. Chart reviews were continued at each site progressing down the list until 40 qualified subjects at each site were identified.

No new treatments or subject observations were conducted as part of this study. Only data recorded by the physician in the course of their normal practice routines were transcribed to CRFs as appropriate.

Eligibility Criteria

Inclusion Criteria

- 1) Treatment with Botox for cervical dystonia under standard practice of medicine
- 2) First [redacted] Botox dose between 1/1/98 and 3/27/98
- 3) Age 18 to 75 during this period
- 4) Patient had received 2 doses of [redacted] Botox at a stable dose prior to [redacted] change-over injection, and received at least 3 doses of [redacted] Botox subsequently, the last one occurring by 10/23/98.
- 5) Patient chart includes adequate information regarding dose

Exclusion Criteria

- 1) Patients with neuromuscular disorder
- 2) Botox treatments for other than CD
- 3) Other investigational study participation during this period, or other Botulinum toxin type had been used.

Study Treatments

Commercial supplies of Botox, both [redacted] and [redacted] were the source of the toxin.

Data Collection

A series of the 5 most recent Treatment cycles in the chart were reviewed; these must be 2 with [redacted] [redacted] toxin followed by 3 with [redacted] toxin. Chart records must have the opportunity for notations regarding sequelae from the first 4 injections (i.e., a patient visit after the injection session). The last injection session need not have any follow-up of patient after recording the dose administered.

For each visit data transcribed to CRFs were:

Date of treatment

Total Dose , with clear identification of the Botox bulk batch source

Clinical response following prior injection; or opportunity to record notes (except dose 5)

Adverse events following prior injection (except dose 5)

Endpoints and Planned Analyses

Primary

Adverse event profile for Botox, with comparison of □[----- to □[----- periods

Secondary

Clinical response characterization

Total Dose used

Analytic Plan

Formal hypothesis testing was not planned for this study. Analysis would be descriptive of the data extracted from the clinic charts.

For Clinical response, a chart which has an explicit notation of lesser response than usual, or of no response, or an otherwise negative comment regarding the quality of response, will be noted as a less than normal response. All other patient chart cycles will be regarded as at least normal response.

STUDY PERFORMANCE AND SUBJECT/CHART DISPOSITION

Enrollment and Disposition

This study was conducted at 11 sites from October 1998 to December 1998. There were 191 charts submitted to Allergan for randomization within site, and then subsequently reviewed. However only 10 of the 11 sites qualified subjects for enrollment into the study.

Of the 11 sites, 4 sites failed to be able to provide the required 60 charts for potential review. Of these, 1 site proposed 37 charts for review, and then upon the subsequent chart review had no subjects qualify for further study inclusion (data extraction). The 10 sites with enrolled (eligible) subjects had 10 to 24 subjects each, except one which enrolled 39 subjects (no site achieved the goal of 40 qualifying subjects). The fraction of qualifying subjects was low overall. To obtain the 191 enrolled subjects there were 713 charts reviewed, for an overall enrollment rate of 26%.

Comment:

One additional site, that of the investigator Perlmutter, was not formally included in this study. CBER had been under the impression from meeting discussions with Allergan that this investigator had conducted his own, prospective, and at least partially blinded, study of comparative effects of □[----- and □[----- Botox that included several score of patients. CBER had thus requested that this site not be included in this study, and instead have the prospective data submitted to CBER in a separate report. The PLA submission actually stated that there had not been any prospective comparison at this site, and that in fact Perlmutter had performed only the same chart review as had been for this study. This site had subsequently found only 11 charts that qualified for the study. These are not included in the report of results.

Protocol Violations

There were 4 sites known to have less than 60 patients to contribute to a subject list, but were permitted to participate due to the low number of qualifying subjects at other sites. There were 4 subjects with booster doses that exceeded the protocol allowance of not more than 25% of the primary dose, and not more than 4 weeks later than the primary dose, but were nonetheless included in the study.

Chart review was not conducted in the randomized order at 7 sites. However, since these sites reviewed all available charts to evaluate eligibility and did not reach the cut off of 40 subjects within their site, they would have reviewed the entire list even if the review had been performed in the randomized order. Thus, this violation had no consequences upon the study.

Demographics

The mean age of enrolled subjects was 55.3 years. Race was designated white for 64%, non-white for 3%, and not recorded for 33%. Female subjects comprised 74% of subjects.

SAFETY RESULTS

There were two serious AE recorded in the charts for the time reviewed. One was a cardiac arrest, one a pneumonia. No details were provided in either study report or CRFs. Both were after initiation of □[----- toxin, however both subjects returned to clinic for at least 1 additional toxin injection session following the adverse event, and received the same dose as at the treatment period prior to the AE.

The incidence as percent of subjects with selected AEs are shown in the following table. Adverse events were selected as those that had shown an association with Botox in prior studies. There were no new types of adverse events with notable incidence not observed in prior studies.

Table 26: Percent Incidence of Subjects with Selected Adverse Events in Study 014						
Adverse Event	Individual Treatment cycle Rates				Combined Cycle Rates	
	[---- Botox		[----- Botox		[---- Botox	□[----- Botox
	Tx 1	Tx 2	Tx 3	Tx 4	Tx 1 or 2	Tx 3 or 4
Neck pain	2	4	4	4	5	7
Dysphagia	2	2	4	5	4	8
Muscle weakness	3	2	5	3	4	6

Comment:

The most notable aspect of these AE results is that the rate of observation and chart notation of dysphagia is twice as high with □[----- Botox as with □[---- Botox. The rates associated with each toxin source are consistent between the two sessions with each type and are generally not occurring in the same subject at the two sessions. While the absolute rates observed in this study cannot be compared to the rates observed in other, prospective studies due to the difference in the manner of AE recording (prospective emphasis vs standard of practice in clinical care), the relative rates between the two toxin preparations within the study are likely to be more reliable. This doubling of the dysphagia rate is the same suggested increase as was seen comparing between Study 140 and Study 004.

DOSE ADMINISTERED RESULTS

Allergan reported the following comparisons of dosing at each treatment session.

Table 27: Average Dose in Successive Treatment Sessions in Study 014		
Treatment Session	Botox Dose (U)	Change from Prior Session (U)
Penultimate [-----	244	
Last [-----	246	1.7
First [-----	248	2.8
Second [-----	251	3
Third [-----	251	-0.7

In total dose, these results are consistent with the dosing amounts observed in prior studies. These results indicate that dosing was stable within in each patient. This suggests that the adverse events observed with [-----] toxin were not of sufficient clinical importance to necessitate a change in dosing for these patients to try to minimize an adverse event.

Comment:

CBER exploration of the dataset for this study, using the full 202 available charts (191 as above with the 11 Perlmutter charts) shows mean doses slightly, but not meaningfully lower than those shown above, with the same pattern of slight increase in dose from each cycle to the next. The time delay between doses was a median of 98 days for all 4 inter-cycle periods except for following the first [-----] dose, when the median was 94 days. The mean delays were generally similar across all cycles (107, 109, 97, 99 days).

SUBJECTIVE RESPONSE RESULTS

The percent of subjects without chart notations indicating a sub-normal response ranged from 88% (first recorded [-----] Botox session) to 93% (second [-----] Botox cycle). The percentages without subnormal response following [-----] Botox cycles (91%, 90%) were bracketed by the two [-----] Botox percentages.